ORIGINAL ARTICLE

HIGH AND INTERMEDIATE-HIGH RISK PULMONARY EMBOLISM MANAGEMENT: A 5-YEAR INTENSIVE CARE UNIT CASUISTIC REVIEW

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Abstract

Background and Objectives: *The optimal management of high-risk and intermediate-high-risk Pulmonary Embolism (PE) is a matter of ongoing debate. This paper aims to assess the short and long-term clinical outcomes associated with different treatment approaches for high-risk and intermediate-high-risk PE within an Intensive Care Unit (ICU) and identify potential areas for improvement.*

Methods: *We conducted a retrospective analysis of patients admitted to an ICU with high and intermediate-high-risk PE between January 2018 and December 2023. The therapeutic approach and clinical outcomes were evaluated: ICU and 28-days survival, ICU and hospital length of stay, major hemorrhagic complications and direct and indirect signs of pulmonary hypertension (PHT). Demographic, comorbid state and severity at admission data were also collected (sex, age, Charlson Comorbidity and APACHE II scores).*

Results: *64 patients were included: 32 high-risk PE (including 18 in cardiac arrest) [Groups 1-5] and 32 intermediate-high-risk PE [Group 6a-c]. Treatment approaches varied: Group 1 - High-risk PE treated with systemic thrombolysis (ST) (n=18); Group 2 - High-risk PE treated with Veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO) plus ST (n=6); Group 3 - High-risk PE treated with VA-ECMO alone (n=5); Group 4 - High-risk PE treated with catheter-direct-therapy (n=1); Group 5 - Heparin only (n=2). Group 1 demonstrated an ICU and 28-day survival of 83.0%, while Groups 2 and 3 exhibited survival rates of 66.67% and 60.0%, respectively. There were 10 major bleeding complications in Group 1 and 2. For intermediate-high-risk PE, heparin alone was used in 90%; ICU and 28-day survival rate was 97%. Three patients exhibited signs of PHT during follow-up.*

Conclusion: *This paper provides insights for the decision-making process involved in managing high and intermediate-high-risk PE drawing from a 5-year retrospective cohort study conducted at an ECMO center and literature review. Further research is needed to identify the specific subgroup within the intermediate-high-risk PE that would benefit from more advanced treatment modalities for both short and long-term outcomes.*

Keywords: *acute pulmonary embolism, pulmonary embolism response team, systemic thrombolysis, Extracorporeal Membrane Oxygenation, chronic thromboembolic pulmonary hypertension.*

INTRODUCTION

Pulmonary Embolism (PE) stands as a life-threatening condition, ranking as the third most common cause of cardiovascular death globally, following myocardial infarction and stroke[1,2]. Given its severity, risk stratification plays a pivotal role in distinguishing patients who can be safely discharged home from those requiring hospitalization or intensive care admission. Short-term mortality varies widely, ranging from 2% in hemodynamically stable patients to 30% in those with right ventricular dysfunction (RVD) and reaching around 80% in patients presenting in cardiac arrest[3,4]. It is crucial to recognize that RVD serves as the primary driver of mortality. The pulmonary thrombus and thrombus-derived vasoconstrictive mediators prompt a significant increase in pulmonary vascular resistance (PVR), leading to acute RV dilation and dysfunction. Furthermore, the pressure overload in the right ventricle induces interventricular septal bowing, impeding left ventricle (LV) preload and eventually compromising overall cardiac

output[3]. Therefore, risk stratification frequently incorporates hemodynamic assessment and the presence of signs of RVD. According to the European Society of Cardiology (ESC) 2019 guidelines, PE is classified into low, intermediate-low, intermediate-high, and high-risk categories. High-risk PE entails hemodynamic instability coupled with signs of RV dysfunction detected by transthoracic echocardiography (TTE) or computed tomography pulmonary angiography (CTPA)[5]. For intermediate-high-risk PE, the guidelines define a hemodynamically stable patient with both RVD, a positive cardiac troponin test, and a class III or IV Pulmonary Embolism Severity Index (PESI) (or simplified PESI $\geq$1). These patients are at a high risk of deterioration, warranting close monitoring to enable timely administration of rescue reperfusion therapy if needed[5].

Beyond patient vigilance and allocation, the importance of risk stratification is inherently linked to the therapeutic approach. It is established that high-risk PE necessitates reperfusion therapy, while low or intermediate-low PE can be managed with anticoagulation alone. However, managing intermediate-high-risk PE poses a challenge: identifying patients who would benefit from upfront reperfusion therapy to prevent further deterioration. Currently, there is no absolute answer, and each case should be individually evaluated in terms of severity, considering factors such as RVD severity, moderate-severe tachycardia, borderline arterial pressure, cardiovascular comorbidities, hypoxia and trends, to weigh the risk/benefit balance of a more aggressive therapy[6].

Moreover, the choice of reperfusion therapy and its timing in cases of severe instability pose additional questions. Treatment options now extend beyond hypocoagulation to include systemic thrombolysis (ST), catheter-directed treatment (CDT), surgical embolectomy, and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as a bridge to recover or further reperfusion therapy[7]. To facilitate the management of high and intermediate-high-risk PE in an individualized and appropriate manner, multidisciplinary teams known as Pulmonary Embolism Response Teams (PERT) are gaining popularity and endorsement[2,8].

This paper focuses on intermediate-high and high-risk PE cases admitted to the Intensive Care Unit (ICU). Our objective is to conduct a retrospective review of the therapeutic approaches chosen by multidisciplinary teams in a tertiary center with experience in VA-ECMO support, cardiothoracic surgery, and interventional radiology, and to examine the short and long-term clinical outcomes.

METHODS

In our retrospective study, we examined patients with high and intermediate-high-risk PE admitted to the Intensive Care Unit (ICU) of a tertiary hospital with VA-ECMO expertise, spanning from January 2018 to December 2023. ESC definition was used for PE classification[5].

The evaluation encompassed the therapeutic approach chosen and both short- and long-term clinical outcomes, specifically ICU and 28-day survival rates, ICU and hospitalization durations, major treatment-associated complications, and the presence of signs of chronic pulmonary hypertension (PHT) or chronic PE on follow-up, when available. The assessment of PHT involved indirect signs identified through transthoracic echocardiography and/or right heart catheterization or pulmonary scintigraphy for chronic PE, conducted during follow-up appointments (at least three months post-hospital discharge). Demographic details, comorbid conditions, and severity at admission were also documented, encompassing sex, age, Charlson Comorbidity Index, and APACHE II scores. All data were sourced from electronic clinical reports, ensuring pseudo-anonymization.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 27 (IBM SPSS Statistics, Armonk, NY). A descriptive analysis was applied, presenting demographic information as median and interquartile range (IQR) or percentage when appropriate.

The study received ethical approval from the local ethics committee (Comissão de Ética do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto).

RESULTS

From January 2018 to December 2023, a total of 64 patients were admitted to an ICU with a diagnosis of either "PE" or "Cardiac Arrest associated with PE." The demographic characteristics of the sample are presented in Table 1. Within this cohort, 32 patients were categorized as high-risk PE, and another 32 as intermediate-high-risk PE. Subsequently, these groups were further stratified based on the primary treatment or management received, as depicted in Figure 1.

High-risk PE:

The "High-risk PE" subgroup was subdivided into five main treatment groups:

Group 1: Patients treated with Systemic Thrombolysis (ST) (n=18); Group 2: Patients managed with both ST and VA-ECMO (n=6); Group 3: Patients managed with VA-ECMO and hypocoagulation, without reperfusion therapy (n=5); Group 4: Patients treated with VA-ECMO and CDT (n=1); Group 5: Patients treated with heparin only (n=2). Table 2 summarizes the results of the high-risk PE cluster, with outcomes presented in median and interquartile ranges (IQR) or units.

Groups 2 and 3 exhibited the highest median APACHE II scores at admission, which was expected, given that most patients in these groups presented with cardiac arrest. However, these groups also displayed the smallest Charlson Comorbidity Indexes, likely indicating a bias in patient selection for VA-ECMO support, favoring younger individuals with fewer comorbidities.

All high-risk PE ICU-survivors were alive 28 days post-

Table 1

	All (n=64)	High risk PE (n=32)	Intermediate-high risk PE (n=32)
Age - median (IQR) Sex - n (%)	61.0 (33.0)	47.0 (32.0)	67.0 (25.0)
Female	41.0 (64.1)	22.0 (68.8)	19.0 (59.4)
Male	23.0 (35.9)	10.0 (31.3)	13.0 (40.6)
Charlson Comorbidity Index - median (IQR)	2.0 (4.0)	2.0 (3.0)	3.0 (4.0)
APACHE II score at admission* - median (IQR)	14.0 (13.0)	19.0 (20.0)	10.5 (9.0)

Demographic characteristics, APACHE II score at admission and Charlson Comorbidity Index of the sample. APACHE - Acute Physiology And Chronic Health Evaluation. IQR - Interquartile Range. PE - Pulmonary Embolism. * 1 missing value for APACHE II score

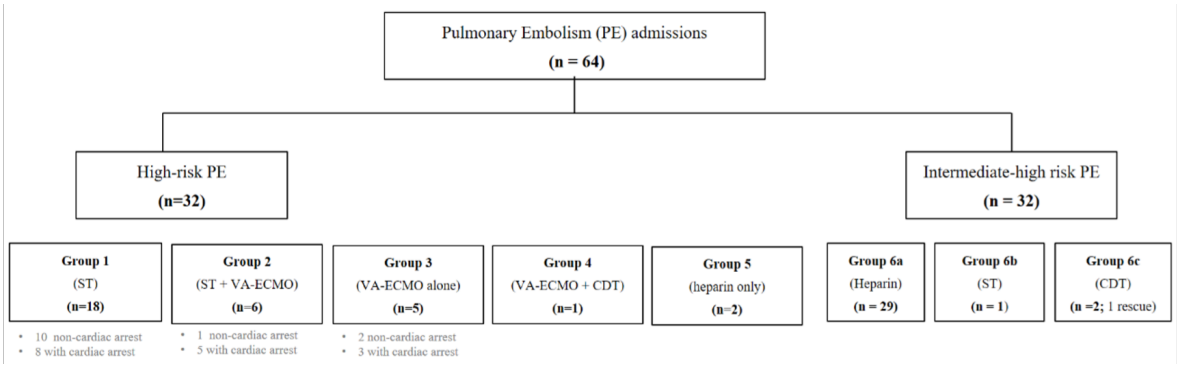

Figure 1

December 2023 in an Intensive Care Unit (ICU). Stratification per risk and division in treatment groups. CDT = Catheter Direct Therapy; CPR = Cardiopulmonary Resuscitation; E-CPR = Extracorporeal Cardiopulmonary Resuscitation; ST = Systemic Thrombolysis; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

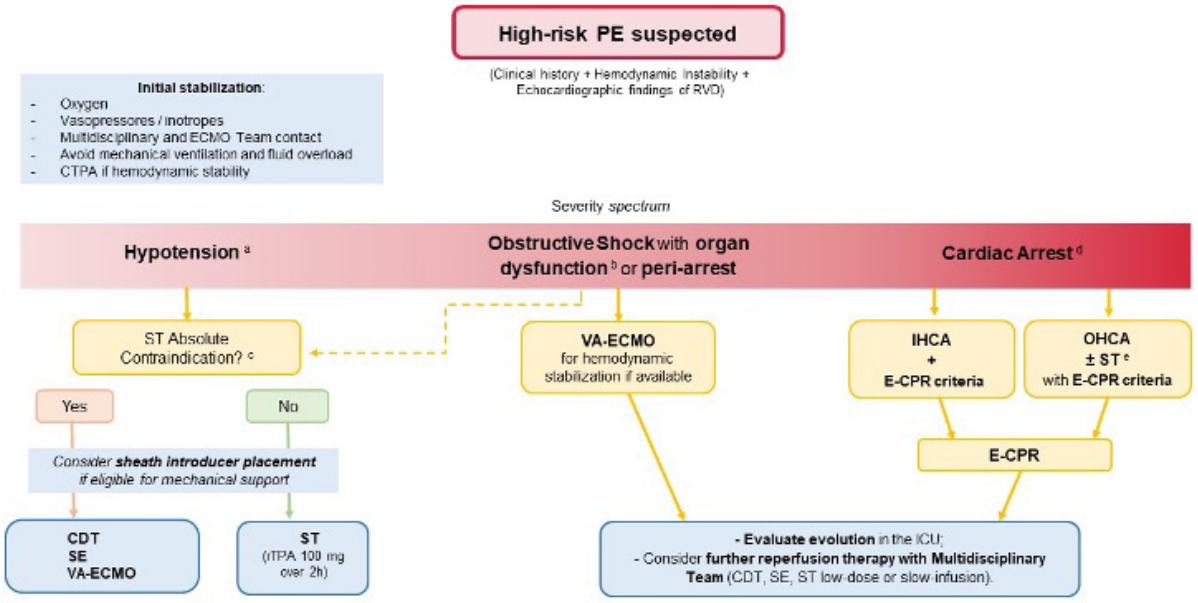

Figure 2

Proposed algorithm for High risk Pulmonary Embolism Management.
a Persistent hypotension (systolic Blood Pressure [BP] <90 mmHg or a systolic BP drop >40 mmHg for >15 min);
b Systolic BP <90 mmHg or vasopressors required to achieve a BP >90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion;
c History of hemorrhagic stroke or stroke of unknown origin; Ischemic stroke <6 months; Central Nervous System Neoplasm; Major trauma/ surgery/ head injury <3 weeks; Bleeding diathesis; Active bleeding (according to the ESC guidelines).
d If IHCA/OHCA without E-CPR criteria, standard cardiopulmonary resuscitation (CPR) with accelerated regimen of ST.
e accelerated regimen (not officially approved; ESC guidelines) -0.6 mg/kg over 15 min (maximum dose 50 mg).
CDT = Catheter Direct Therapy; CTPA – Computed Tomography Pulmonary Angiogram; E-CPR = Extracorporeal Cardiopulmonary Resuscitation; IHCA – Intra-Hospital Cardiac Arrest; OHCA – out of Hospital Cardiac Arrest; PE – Pulmonary Embolism; rtPA – alteplase; RVD – Right Ventricular dysfunction; SE – Surgical Embolectomy; ST = Systemic Thrombolysis; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

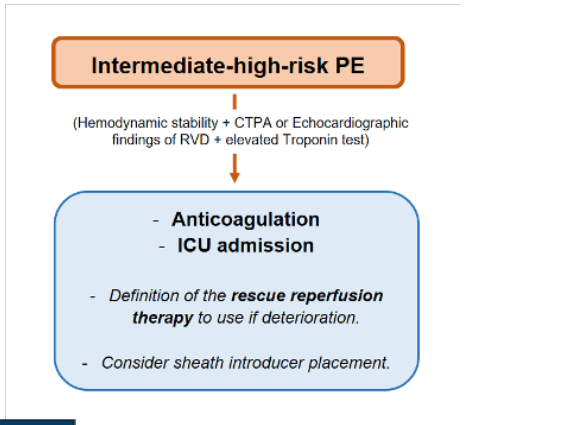

Figure 3

Proposed algorithm for Intermediate-high risk Pulmonary Embolism Management. Rescue therapy should be defined at admission considering patient bleeding risk, if there are systemic thrombolysis contraindications and the feasibility of other options like catheter-direct-therapy. Reduce dose and slow infusion of alteplase may be considered. If severe RVD or in uncertain cases, consider sheath introducer placement for a possible veno-arterial extracorporeal membrane oxygenation (VA-ECMO) cannulation. CTPA – Computed Tomography Pulmonary Angiogram; PE – Pulmonary Embolism; RVD – Right Ventricular dysfunction.

hospital discharge, with a survival percentage of 75.8%. Notably, half of this cluster experienced cardiac arrest at presentation (n=16), as detailed in Table 3. The majority of cardiac arrests were intra-hospital (IHCA), yet all patients received immediate support from intra or pre-hospital teams, minimizing the "no flow" time. Half of these patients were treated with ST with a survival of 62.5%; the "low flow" time of theST-treated patients was relatively shorter. Seven patients entered the extracorporeal cardiopulmonary resuscitation (E-CPR) program (inclusion criteria in the supplementary data 1) because of refractory cardiac arrest (higher "low flow" time). Among the E-CPR patients, three had undergone ST before cannulation, one post-cannulation, and three (Group 3) did not undergo ST, primarily due to major contraindications. Despite achieving hemodynamic stability in all E-CPR patients, three patients had severe cerebral hypoxic-ischemic lesions, leading to treatment withdrawal. One patient (Group 2) initiated VA-ECMO support after achieving return of spontaneous circulation (ROSC) due to refractory cardiogenic shock and hemodynamic instability (see supplementary table 1 for details).

All patients without cardiac arrest at presentation were alive 28 days post-hospital discharge. The majority were treated with ST (Group 1), except for one patient who remained hemodynamically unstable post-ST and initiated VA-ECMO support (Group 2) and three patients with absolute contraindications for ST and were started on VA-ECMO (two without further reperfusion therapy - Group 3 - and one with CDT after stabilization – Group 4). Two patients treated with heparin only (Group 5) had absolute contraindications for ST and were deemed unsuitable for other treatments by the multi-disciplinary team.

Regarding major hemorrhagic complications (intracranial bleeding, intra-abdominal bleeding, or bleeding necessitating ≥3 blood component transfusions), in High-Risk PE, they were more frequent in Group 2, with half of the patients experiencing them, and in Group 1 (despite a higher n). In two patients in Group 1 with major hemorrhagic complications, ST had been administered despite absolute contraindications: one patient had a subacute subdural hematoma and the other was in the post-operative period. The patient with the subdural hematoma, was initially proposed for CDT but, due to sudden deterioration, ST was administered as life-saving therapy. The patient in the post-operative period was not considered for ECMO support due to his frailty, and ST was given as life-saving therapy, in a center without CDT availability.

Lastly, we did not find indirect signs of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) at follow-up, in the high-risk PE survivors, however, there were many missing values (7 in 25 survivors).

Intermediate-high-risk PE

The intermediate-high-risk PE group was further subdivided into three main groups:

Group 6a: Treated with heparin only (n=29); Group 6b: Treated with ST (n=1); Group 6c: Treated with CDT (n=2).

The ICU and 28-day after discharge survival for this cluster was 96.5%. In Group 6b, where ST was employed off-label due to intra-cardiac thrombus, the patient received an ultra-slow low-dose of tissue plasminogen activator (1 mg/h) in combination with heparin. In Group 6c, CDT was used in conjunction with ST as a rescue therapy after hemodynamic deterioration at 48 hours and as primary therapy for one patient with a high clot burden associated with Antiphospholipid Syndrome (APS). This patient subsequently developed CTEPH, confirmed by right heart catheterization and ventilation/perfusion scintigraphy. In the heparin-only group (Group 6a), one other patient exhibited signs of Pulmonary Hypertension (PHT) on follow-up echocardiography, with elevated pulmonary systolic pressure, low deceleration time, and right ventricle dysfunction and another one, presented with signs of chronic PE on ventilation/perfusion scintigraphy.

No major bleeding complications were observed in the intermediate-high risk PE.

Eight cases (3 intermediate-high-risk and 5 high-risk PE) involved preemptive sheath introducer placement by the assistant team for expedited VA-ECMO cannulation if needed before ST or heparin use. None of these patients required cannulation, and no major complications arose from this procedure.

DISCUSSION

High-risk PE

The mortality rates associated with high-risk PE remain unacceptably elevated, reaching 46% in patients in

Table 2

	High risk PE All (n=32)	Group 1 ST (n=18)	Group 2 ST + ECMO (n=6)	Group 3 ECMO alone (n=5)	Group 4 ECMO + CBT (n=1)	Group 5 Heparin only (n=2)
APACHE II at admission – median (IQR) [or score]	19.0 (20.0)	16.0 (17.0)	34.0 (15.0)	23.0 (10.0)	4.0	24.0; 9.0
Charlson index - median (IQR) [or score]	2.0 (3.0)	2.0 (3.0)	0.5 (1.0)	0.0 (4.0)	0.0	0.0; 9.0
ICU survival - n (%)	25 (75.8)	15 (83.3)	4 (66.7)	3 (60.0)	1 (100)	2 (100)
Hospital survival – n (%)	25 (75.8)	15 (83.3)	4 (66.7)	3 (60.0)	1 (100)	2 (100)
28-day survival – n (%)	25 (75.8)	15 (83.3)	4 (66.7)	3 (60.0)	1 (100)	2 (100)
ICU length of stay – median (IQR) [or days]	5.5 (11.0)	5.0 (5.0)	9.0 (27.0)	9.0 (43.0)	34.0	3.0; 8.0
ECMO-days - median (IQR; or days)	-	-	3.0 (5.5)	5.0 (11.0)	12.0	-
Hospital length of stay – median (IQR) [or days]	15.5 (29.0)	12.0 (17.0)	29.0 (39.0)	34.0 (68.0)	48.0	6.0; 56.0
Major hemorrhagic complications – n (%)	11 (34.4)	7 (38.9)	3 (50.0)	0 (0)	1 (100)	0 (0)
Signs of PH at follow-up – n (%)*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Characterization of high-risk Pulmonary Embolism by treatment group in terms of APACHE II at admission, survival, length of stay and complications. APACHE - Acute Physiology And Chronic Health Evaluation; CBT – Catheter based thrombolysis; ICU – Intensive Care Unit; IQR - Interquartile Range. PE - Pulmonary Embolism; PH – Pulmonary Hypertension; ST – systemic thrombolysis; (VA-)ECMO – Veno-arterial Extracorporeal Membrane Oxygenation. Scores and length of stay of Group 4 and 5 are expressed in units. *7 missing values for signs of PHT at follow-up (4 in group 1; 2 in group 2; 1 in group 5).

shock and escalating to 84% in those with cardiac arrest[4]. In our examined sample, the mortality rate for high-risk PE was relatively low at 21.8%, considering that half of the high-risk PE patients were in cardiac arrest upon presentation. It's important to note the limitations of our study, including the small sample size and potential selection bias related to patients admitted to the ICU (in terms of cardiac arrest duration and premorbid patient states). Despite these limitations, we aim to delve into the treatment strategies employed in this restricted sample. Our intention is to open the discussion around new therapeutic approaches and avenues for further investigation. Understanding the challenges posed by high-risk PE mortality rates, even within a constrained dataset, can contribute to the development of innovative and more effective treatment methodologies.

Spectrum of severity of High-risk PE

Systemic thrombolysis (ST) indeed holds a well-established position as the first-line therapy for patients with high-risk PE without absolute contraindications, aligning with both European and American guidelines[5,9]. Consistent with these recommendations, our data indicates that Group 1 (ST) exhibited a relatively high survival percentage. However, high-risk PE presents a spectrum of severity, ranging from hypotension to cardiogenic shock and to cardiac arrest. In the context of cardiac arrest, the effectiveness of ST is compromised, likely due to circulatory collapse and reduced contact between the lytic agent and clot burden[10]. In such cases, circulatory support with VA-ECMO emerges as a potential life-saving intervention, showing a survival benefit. Current guidelines suggest the use of VA-ECMO in cardiac arrest cases, albeit with a low-grade recommendation.[5] A recent extensive German database focusing on ECMO utilization for PE supports this, indicating that patients with cardiopulmonary resuscitation (CPR) benefit from VA-ECMO, either alone or in combination with other reperfusion strategies if hemodynamic compromise persists.[11] Within our sample, patients experiencing cardiac arrest predominantly initiated VA-ECMO as part of extracorporeal CPR (E-CPR) and following attempted ST. As a result, the "low flow" times in ECMO patients were higher compared to the ST group, with over 30 minutes in three of the four ECMO patient survivors,

whereas ST patients experienced less than 20 minutes. It is noteworthy that extended "low flow" times increase the risk of severe cerebral hypoxic lesions. Consequently, in cases of cardiac arrest, there may be a potential benefit in instituting early VA-ECMO support, foregoing the wait for the efficacy of ST boluses. Furthermore, in instances where ST is contraindicated, VA-ECMO can be promptly implemented as a bridge for recovery or for subsequent reperfusion therapies such as catheter-directed treatment (CDT) or surgical embolectomy (SE).

Besides cardiac arrest, VA-ECMO might still have an important role in stabilizing patients in cardiogenic shock. Indeed, there is a sound physiological rationale for employing VA-ECMO in hemodynamically unstable PE. Given that RV failure is a primary contributor to instability in PE [12], VA-ECMO not only provides circulatory support and gas exchange but also interrupts the "RV death spiral" by unloading it. Through a circuit that draws blood from the right atrium and returns it to the arterial circulation, VA-ECMO creates a bypass to the RV, reducing end-diastolic volume and pressure, as well as RV myocardial oxygen consumption. Survival outcomes for patients with extracorporeal life support (ECLS) initiated specifically for high-risk PE tend to be superior when compared to the initiation of ECLS for other reasons.[13]

According to the supplementary emergency management Algorithm outlined in the 2019 ESC guidelines, VA-ECMO is recommended before reperfusion therapy if early hemodynamic stabilization is not achieved. It is subsequently combined with surgical or catheter embolectomy.[5] A recent large American report on ECMO use in massive PE also emphasizes the importance of avoiding delays in VA-ECMO placement in cases of severe hemodynamic instability, as the mode "E-CPR" was associated with higher in-hospital mortality.[14] In our sample, five cases involved VA-ECMO placement without previous cardiac arrest – two due to persistent instability after systemic thrombolysis (ST) and three due to ST contraindications. Encouragingly, all of these cases survived. It is important considering circulatory support as an early option for patients in shock or with ST contraindications. While CDT and SE are effective, they may require patient transport and time for execution. In such cases, VA-ECMO serves as a bridge to subsequent interventions.

There is residual evidence supporting the use of VA-ECMO as a bridge to recovery in certain cases, where a proportion of patients may experience recovery from RV failure and overall shock with VA-ECMO and anticoagulation alone, without the need for further reperfusion therapy, typically within a mean of 5 days[9]. Although evidence for this approach is limited, some experienced centers have reported optimistic results in retrospective studies, demonstrating good survival rates across various contexts and severity levels, including cases where VA-ECMO was employed as a rescue therapy, during E-CPR, or in severe cardiogenic shock[15-17]. However, it is important to note that other retrospective studies present less favorable outcomes for this strategy when compared with SE performed in a semi-elective fashion after the initiation of VA-ECMO[18,19]. In your sample, the number of patients undergoing VA-ECMO without reperfusion therapy (Group 3) is limited. Aside from the two cardiac arrest patients with severe hypoxic-ischemic encephalopathy, the other three survived with no major hemorrhagic complications. The relatively small sample size emphasizes the need for further investigation and larger-scale studies to better understand the outcomes and potential benefits or limitations associated with VA-ECMO as a bridge to recovery without additional reperfusion therapy.

Bleeding complications

The consideration of bleeding complications, particularly intracranial bleeding, is important when treating high-risk PE patients with systemic thrombolysis (ST), as it can significantly impact functional outcomes and the length of hospital stay. In this limited sample, major bleeding complications were observed frequently in both Group 1 and Group 2, with a higher relative weight in Group 2. This heightened occurrence in Group 2 might be attributed to the synergistic bleeding risk introduced by VA-ECMO in patients who have already undergone thrombolysis.

Given concerns about bleeding complications, there has been ongoing research to establish optimal ST dosing. However, high-quality evidence regarding the dose, infusion rate, or alternative approaches to fixed doses of tissue Plasminogen Activator (t-PA) (e.g., weight-based dosing or titration based on physiological effects and coagulation tests) is lacking. Emerging evidence suggests the efficacy of lower-dose ST in acute PE[20,21]. Despite this, a large retrospective study in 2018 showed no benefit in half-dose alteplase compared to the full dose[22]. In this sample, full-dose t-PA (100 mg IV alteplase in 2h) was uniformly used in all cases of high-risk PE, or boluses of 20-50 mg in cardiac arrest. Exploring lower doses may offer a potential avenue to reduce bleeding complications, especially if further reperfusion therapies, such as SE or VA-ECMO placement for hemodynamic stabilization, are anticipated.

Another potential strategy for reducing bleeding complications could be the use of VA-ECMO in severely unstable patients without prior ST. This approach involves evaluating the need for further reperfusion therapy after the initial stabilization, as discussed earlier. Currently, evidence supporting this approach comes from retrospective analyses of cases with contraindications to ST.

Additionally, preemptive sheath introducer placement for VA-ECMO cannulation prior to ST use, could be another approach for possibly avoiding major bleeding, as occasionally done in this cohort. There is no clear literature on this practice, as far as we know. In this cohort, the strategy was a proactive measure taken in dubious cases where VA-ECMO support might be needed as rescue therapy. The preemptive sheath introducer placement had no serious side effects. None of the cases ultimately required VA-ECMO. This strategy, while not yet extensively documented, might be a

Table 3

	PE with Cardiac Arrest (All) (n=16)	Group 1 ST (n=8)	Group 2 ST + ECMO (n=5)	Group 3 ECMO alone (n=3)
APACHE II at admission – median (IQR; or min, max)	29.0 (20.0)	25.0 (18.0)	36.0 (21.0)	26.0 (min 22; max 31)
Type of Cardiac arrest				
OHCA	3	2	1	0
IHCA	13	6	4	3
Cardiac arrest duration (low flow), minutes – median (IQR; or min, max)	32.5 (39.0)	8.50 (45.0)	40.0 (26.0)	38 (min 35, max 45)
Survivors	-	Min 4.0; max 20.0	Min 10.0; max 48.0	45.0
No survivors	-	Min 7.0; max 60.0	Min 40.0; max 44.0	Min 35.0, max 38.0
If VA-ECMO:				
In context E-CPR	6	-	4	3
Post ROSC	1	-	1	0
ECMO-days - median (IQR; or min, max)	-	-	3.0 (2.0)	3.0 (min 2, max 14)
ICU survival - n (%)	9 (56.2)	5 (62.5)	3 (60.0)	1 (33.3)
28-day survival – n (%)	9 (56.2)	5 (62.5)	3 (60.0)	1 (33.3)
ICU length of stay – median (IQR; or min, max)	5.5 (12.0)	5.5 (13.0)	9.0 (17.0)	3 (min 2, max 41)
Hospital length of stay – median (IQR; or min, max)	22.0 (34.0)	14.0 (34.0)	26.0 (32.0)	34 (min 2, max 87)
Major hemorrhagic complications – n (%)	6 (35.3)	5 (62.5)	3 (60.0)	0 (0)

Characterization of High risk Pulmonary Embolism with cardiac arrest at presentation, by treatment group in terms of APACHE II at admission, survival, length of stay and complications. APACHE - Acute Physiology And Chronic Health Evaluation; ICU – Intensive Care Unit; IQR - Interquartile Range. PE - Pulmonary Embolism; ST – systemic thrombolysis; VA-ECMO – Veno-arterial Extracorporeal Membrane Oxygenation. OHCA – out of hospital cardiac arrest; IHCA – intra-hospital cardiac arrest; ROSC – return of spontaneous circulation.

prudent consideration for evading potential bleeding risks associated with VA-ECMO cannulation following ST. Further research and exploration of these strategies are warranted to establish their efficacy and safety conclusively.

Long-term outcomes

There is limited data about long-term outcomes of high-risk PE, namely the presence of PHT[4]. In this sample, none of the high-risk PE survivors had signs of PHT at follow-up, which might indicate complete thrombus dissolution with the instituted treatments.

Intermediate-high Risk PE

Intermediate-high-risk PE presents distinct challenges and considerations in treatment compared to high-risk PE. Mortality rates for intermediate-high-risk PE range from 3 to 14%[23], consistent with your sample's mortality rate of 3.1%. Current management typically involves anticoagulation and close monitoring for rapid hemodynamic stabilization if decompensation occurs. However, the optimal treatment approach remains controversial.

The consideration of ST as an upfront intervention for intermediate-high-risk PE is debated. While some experts argue that upfront ST could prevent hemodynamic collapse and death[24], the considerable bleeding risk, including up to 10% serious bleeding and 1.5% intracranial hemorrhage[3], poses a challenge. Trials like PEITHO have explored the effects of ST followed by anticoagulation but did not show a favorable risk/benefit balance (significant reduction on hemodynamic collapse but the major bleeding risk unacceptably high)[25]. Subgroups are being studied to identify potential candidates for reduced-dose ST (alteplase 0.6 mg/kg to a maximum of 50 mg), as seen in the ongoing PEITHO-3 trial.[26]

In this cohort, ST was employed upfront in intermediate-high risk PE in one patient with an ultra-slow

Table 4

	Intermediate-high risk PE (All) (n=32)	Group 6a Heparin (n=29)	Group 6b ST (n=1)	Group 6c CDT (n=2)
APACHE II score at admission* - median (IQR)	10.5 (9.0)	10.0 (9.0)	10	11, 17
Charlson index - median (IQR) [or score]	3.0 (4.0)	3.0 (4.0)	2	0
ICU survival - n (%)	31 (96.9)	28 (96.5)	1 (100)	2 (100)
Hospital survival – n (%)	31 (96.9)	28 (96.5)	1 (100)	2 (100)
28-day survival – n (%)	31 (96.9)	28 (96.5)	1 (100)	2 (100)
ICU length of stay – median (IQR)	3.0 (3.0)	2.0 (3.0)	14	4.0; 38.0
Hospital length of stay – median (IQR)	7.0 (8.0)	7.0 (5.0)	20.0	9.0; 60.0
Major hemorrhagic complications – n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Signs of PHT – n (%)*	3 (9.4)	2 (6.9)	0 (0)	1 (50.0)

Characterization of intermediate-high risk Pulmonary Embolism by treatment group in terms of APACHE II at admission, survival, length of stay and complications. APACHE - Acute Physiology And Chronic Health Evaluation; CBT – Catheter based thrombolysis; ICU – Intensive Care Unit; IQR - Interquartile Range. PE - Pulmonary Embolism; PHT – Pulmonary Hypertension; ST – systemic thrombolysis. Scores and length of stay of Group 6b and 6c are expressed in units. *3 missing values for signs of PHT at follow-up.

dose of t-PA[27] in the context of an intracardiac thrombus and in conjunction with CDT in a subacute intermediate-high risk PE in a patient with APS. ST was also used as rescue therapy (in conjunction with CDT) in one patient who deteriorate on heparin-only management.

Lastly, it is essential to discuss the relatively high number of signs of PHT observed during follow-up in the intermediate-high-risk PE patients in this sample. Chronic Thromboembolic Pulmonary Hypertension (CTPH) is a relatively rare condition, occurring in an estimated 3% of patients with a previous PE[28]. In our sample, we collected indirect signs of PHT through echocardiography or chronic PE in pulmonary scintigraphy, as well as direct signs through right heart catheterization during follow-up appointments. One patient had CTPH confirmed, another exhibited echocardiographic indirect signs of PHT, and another signs of chronic PE on pulmonary scintigraphy. It is recognized that intermediate-risk PE is more strongly associated with CTEPH compared to high-risk PE[29]. Previous suggestions proposed that this association could be explained by the more complete dissolution of emboli in patients undergoing reperfusion therapies compared to those treated with anticoagulation alone. The MOPETT trial investigated whether a half-dose of t-PA would reduce rates of PTH (as assessed by echocardiogram) at 28 months, revealing a significant difference between ST and heparin-only groups without an increase in bleeding[30]. However, the incidence of PHT in this trial was incongruent with previous reports[3]. Moreover, in the PEITHO trial long-term analysis, ST did not appear to reduce RV dysfunction at follow-up for intermediate-high risk PE patients[31]. Hence, whether our results can be justified by the use of anticoagulation-only in these patients or not remains a matter of debate. Further investigation into risk factors and treatment strategies to avoid PHT is warranted.

This study contributes to the scientific community by sharing the results from an ICU of a tertiary-care hospital with ECMO experience in treating high and intermediate-high-risk PE, aiming to stimulate discussion on new therapeutic strategies and areas for improvement. Based on the insights from this cohort analysis and literature review, two algorithms are proposed to guide the decision-making process for managing high and intermediate-high risk PE (Figure 2 and 3).

We acknowledge the methodological limitations of this work as a retrospective study with a small sample. Given the retrospective nature of the data, specifying exact timings of procedures and the treatment rationale applied poses challenges.

CONCLUSION

High and intermediate-high risk PE patients present a wide spectrum of severity and treatment options. Consequently, the management of these cases requires a multidisciplinary approach. This paper reflects on the decision-making process in managing high and intermediate-high risk PE through a 5-year retrospective cohort study conducted at an ECMO center. Further research is needed to identify the specific subgroup within the intermediate-high-risk PE that would benefit from more advanced treatment modalities for both short and long-term outcomes.

SUPPLEMENTARY DATA

Inclusion Criteria for Extracorporeal Cardiopulmonary Resuscitation (E-CPR)

A) Patient-related variables (both present):
- Age between 18 and 60 years;
- Absence of important comorbidities (e.g. advanced chronic organ insufficiency: renal, hepatic or advance heart failure; advance lung disease)..

B) Cardiac arrest variables (at least one present):
- Shockable rhythm on first assessment;
- Evidence of pulmonary embolism, hypothermia or acute intoxication.

C) Cardiopulmonary resuscitation (CPR) variables (all present):
- Cardiac arrest witnessed and promptly assisted;
- Time of cardiac arrest until advance life support < 10 minutes;
- Time of advance life support until the beginning of cannulation between 10-30 minutes;
- Transport to the hospital with mechanical compressions in case of out of hospital cardiac arrest.

Note: the program started in 2017 and minor changes might have occurred during the years.

Supplementary Table 1

VA-ECMO implementation rational:	Outcome
Group 2	
No cardiac arrest	
A 34-year-old female patient was transferred from another hospital one day after receiving systemic thrombolysis (ST). Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was initiated due to ongoing hemodynamic instability. Decannulation was performed after 17 days.	Survived One major bleeding complication
Cardiac arrest	
A 25-year-old female patient experienced a cardiac arrest within the emergency service, promptly receiving assistance and undergoing cannulation for E-CPR (low-flow time of 30 minutes). PE was suspected and confirmed after cannulation, leading to the administration of 90 mg of alteplase. Decannulation was performed after 3 days.	Survived No major bleeding
A 29-year-old female patient was admitted to the emergency service for high-risk PE and received a dose of 10 mg followed by 90 mg of alteplase over a 2-hour period. Despite this intervention, the patient's hemodynamic status did not improve, leading to cardiac arrest and prompt cannulation for E-CPR with a low-flow time of 10 minutes. Decannulation was performed after 3 days.	Survived No major bleeding
A 50-year-old male patient was admitted to the emergency service due to high-risk pulmonary embolism (PE) with an intra-hospital cardiac arrest. Despite the administration of 10 mg followed by 80 mg of alteplase, the patient experienced refractory cardiac arrest, leading to the initiation of extracorporeal cardiopulmonary resuscitation (E-CPR) with a low-flow time of 44 minutes.	Died (severe hypoxic encephalopathy) No major bleeding
A 22-year-old female patient was transferred for the initiation of VA-ECMO due to persistent hemodynamic instability. This followed a cardiac arrest with return of spontaneous circulation (ROSC) achieved through the administration of 50 + 50 mg of alteplase as part of the cardiopulmonary resuscitation (CPR). She was deemed unsuitable for catheter-based therapy (CBT) in the previous hospital. The low-flow time during the event was 40 minutes.	Died (refractory shock; multi-organ failure) Major bleeding complication
A 37-year-old female patient experienced an out-of-hospital cardiac arrest (OHCA), promptly receiving support from the medical team at the airport and pre-hospital team before being transported to the hospital. In the pre-hospital setting, 50 mg of alteplase was administered, followed by an additional 50 mg upon arrival at the hospital. E-CPR was initiated due to refractory cardiac arrest, with a low-flow time of 48 minutes. VA-ECMO decannulation was possible after 4 days.	Survived Several major bleeding complications

VA-ECMO implementation rational:	Outcome
Group 3	
No cardiac arrest	
A 69-year-old female patient experienced an in-hospital high-risk PE with an absolute contraindication for ST due to recent neurosurgery. VA-ECMO was initiated for hemodynamic stabilization. Right ventricular dysfunction (RVD) resolved without additional therapy, aside from heparin, making decannulation possible after 13 days.	Survived No major bleeding
A 60-year-old female patient, post-operative from orthopedic surgery, developed a highly unstable PE with an absolute contraindication for ST due to her postoperative status. She was cannulated for VA-ECMO during a peri-arrest period at the time of cannulation. Decannulation was successfully performed within 5 days.	Survived No major bleeding
Cardiac arrest	
A 22-year-old male patient, admitted to neurocritical intensive care due to severe traumatic brain injury (TBI), experienced an intra-hospital cardiac arrest (IHCA) because of PE. Despite prompt CPR, the ECMO team was activated late, resulting in at least 45 minutes of low-flow time. ST was not administered due to the presence of TBI. Decannulation was successfully achieved within 14 days.	Survived No major bleeding
A 25-year-old male patient, experiencing an extended hospital stay due to Guillain-Barré syndrome, suffered an IHCA following a tonic-clonic seizure. CPR was promptly initiated, and the ECMO team was activated for E-CPR due to refractory cardiac arrest (low flow time of 38 minutes), resulting in hemodynamic stabilization. The diagnosis of PE was established after cannulation; ST was not attempted during CPR.	Died (severe hypoxic encephalopathy) No major bleeding
A 47-year-old female patient experienced an IHCA at the emergency department. Prompt CPR was initiated, and E-CPR was initiated with a low flow time of 35 minutes, achieving hemodynamic stability. Despite these efforts, the patient exhibited clinical, encephalographic, and imagiological indicators of a poor prognosis. As a result, the treatment was withdrawn.	Died (severe hypoxic encephalopathy) No major bleeding
Group 4	
A 34-year-old female patient, post-operative, developed a high-risk PE. ST was contraindicated due to recent surgery. CBT was attempted, but it failed to achieve hemodynamic stability. Consequently, VA-ECMO was initiated and continued for a duration of 12 days.	Survived One major bleeding

Rational of each VA-ECMO implementation. Some inconsistencies might exist as the data is derived from retrospective reports.

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